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Formulation and Evaluation of Controlled Release Matrix Tablet of A Model Antibiotic Drug

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ABSTRACT

The concept of controlled release tablet can be utilized to provide a long lasting and more reliable release of drug in GIT to ultimately develop a once daily formulation. Thus, they prolong the dosing intervals, but also increase patient compliance beyond the level of existing conventional dosage forms. Erythromycin, macrolide antibiotics is used in the treatment of Mycoplasma pneumoniae infections, Chlamydial infections, etc. It is a drug with short biological half-life 1.5 hrs and dosing frequency more than one per day which makes it an ideal candidate for controlled release. The present investigation was planned to formulate the Erythromycin stearate once daily controlled release tablets. The tablets were prepared by direct compression method and were subjected for *in vitro* drug release studies. The mechanism of drug release was determined using various kinetic models. The results revealed that all the formulated tablets had acceptable physical properties and showed release up to 24 hrs. The kinetic studies revealed that all the formulations followed Zero order release kinetics. The tablets were prepared by Direct Compression technique and evaluated for various parameters. The optimized formulation contains Erythromycin Stearate as active ingredient, HPMC K15M, Chitosan and Xanthan gum as rate retarding polymers.

Keywords: Erythromycin stearate, Matrix tablets, Controlled release, Chitosan, Hydroxy propyl methyl cellulose, Direct Compression.

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INTRODUCTION

Controlled release system[1, 2]

In recent years, considerable attention has been focused on the development of controlled drug delivery systems. The basic rationale of controlled drug delivery system is to optimize the Biopharmaceutics, pharmacokinetic and pharmacodynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of conditions, in the shortest possible time by using smallest quantity of drug administered by most suitable route[3].

In general, controlled drug delivery attempts to[4]:

- Sustain drug action at predetermined rate by maintaining constant and effective drug level in the body with concomitant minimization of undesirable side effects associated with saw tooth pharmacokinetic pattern.
- Localize the drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or organ.
- Target drug action by using carriers or chemical derivatization of drugs to a particular target.

An ideal controlled drug delivery system delivers the drug at a predetermined rate, locally or systemically for a specified period of time[5]. Controlled drug delivery system not always releases the drug by zero order kinetics. It may release by first order or any other kinetic model.

Oral Drug Delivery and Delivery Systems[6]:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes that have been explored for the systemic delivery of drugs in case of different dosage forms. The oral controlled-release system is usually made of polymers, and the mechanisms of release are generally regulated by diffusion, bioerosion or degradation, and swelling or generation of osmotic pressure. Diffusion occurs when the drug–polymer mixture is exposed to the gastrointestinal fluid, resulting in release of the drug from the tablet or capsule. Bioerosion or degradation occurs with certain polymer-drug complexes when they pass through the gastrointestinal tract. Swelling or generation of osmotic pressure occurs with certain polymer-drug formulations when they are exposed to the gastrointestinal fluid, resulting in the release or expulsion of the drug. Controlled release systems are usually involved in prolonging the drug dissolution, producing more reliable absorption and to improve the bioavailability and efficacy of delivery.

Oral controlled drug delivery[7,8]:

Oral controlled-release drug delivery is thus a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit.

In the exploration of oral controlled release drug administration, one encounters three areas of potential challenges:

1. **Development of a drug delivery system[9]:** To develop a viable oral controlled release drug delivery system capable of delivering a drug at a therapeutically effective rate to a desirable site for duration required for optimal treatment.
2. **Modulation of gastrointestinal transit time[9]:** To modulate the GI transit time so that the drug delivery system developed can be transported to a target site or to the vicinity of an absorption site and reside there for prolonged period of time to maximize the delivery of a drug dose.
3. **Minimization of hepatic first pass metabolism[9]:** If the drug to be delivered is subjected to extensive hepatic first pass metabolism preventive measures should be devised to either bypass or minimize the extent of hepatic metabolic effect.

The controlled release systems for oral use are mostly solid and based on dissolution or diffusion or a combination of both the mechanisms in the control of release rate of drug.

Depending upon the manner of drug release, they are classified as:

A. Continuous release system[10,11]*:* These systems release the drug for a prolonged period of time along the entire length of GI tract with normal transit of the dosage form. The various systems under this category are:

I. Dissolution controlled release systems

II. Diffusion controlled release systems

III. Dissolution and diffusion controlled release systems

IV. Ion-Exchange resins-drug complexes

V. Slow dissolving salts and complexes

VI. pH-dependent formulations

VII. Osmotic pressure controlled systems

VIII. Hydrodynamic pressure controlled systems

B. Delayed transit and continuous release system[10,11]: These systems are designed to prolong their residence in the GI tract along with their release. Often, the dosage form is fabricated to

retain in the stomach and hence the drug present therein should be stable at gastric pH. Systems included in this category are:

I. Altered density systems

II. Mucoadhesive systems

III. Size-based systems

C. Delayed release systems[10, 11]: The design of such systems involve release of drug only at a specific site in the GI tract.

The drugs contained in such systems are:

I. Intestinal release systems

II. Colonic release systems

With recent advances in oral delivery technology, many more opportunities for treatment are available such as local therapy in the GI tract, delivery of macromolecules using mucoadhesive compounds and permeation enhancers with site specific targeting. Absorption rates may be altered by using controlled release formulations to increase the residence time of a drug.

MATERIALS AND METHODS

Erythromycin stearate (S Kant Healthcare Ltd, Vapi); Xanthan gum(CP Kelico, New Zealand); Hypromellose(Dow Chemicalsn Midland, Michigan, US); Micro crystalline cellulose (FMC BioPolymer, Philadelphia, U.S.); Chitosan(LINCOLN PHARMA, Ahmedabad, India); Sodium alginate(S Kant Healthcare Ltd, Vapi) and Hydroxy Ethyl Cellulose(S Kant Healthcare Ltd, Vapi). All chemicals and solvents used were of analytical grade.

Pre-compression studies:

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. The objectives of pre-formulation studies are to develop a portfolio of information about the drug substance, so that this information is useful to develop formulation. Following are the tests performed for the pre-formulation study.

Determination of bulk density[12,13]

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}} \qquad \text{--------- (a)}$$

$$TBD = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}} \qquad \text{---------- (b)}$$

Determination of Tapped density[12,13]

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρt) was calculated using the following formula;

$$\rho_t = \frac{M}{V_t}$$

Carr's compressibility index & Hausner's Ratio[14]

An important measure that can be obtained from bulk density determinations is the percent compressibility C, grading of the powders for their flow properties.

$$\text{Carr's Index (\%)} = \frac{TBD - LBD}{TBD} \times 100 \qquad \text{----- (c)}$$

Hausner's ratio[14]

Hausner's ratio is an indirect index of ease of measuring the powder flow. Flow properties according to Hausner's ratio is calculated by the following formula:

$$\text{Hausner ratio} = \frac{\rho_t}{\rho_d}$$

Angle of repose[15]

The angle of repose of the powder blend was determined by using funnel method. The diameter of the powder cone was measured and angle of repose was calculated by using the equation

$$\tan \theta = \frac{h}{r}$$

Where h and r are the height of pile and radius of the base of pile

Preparation of Matrix tablets

The Matrix tablets were fabricated by direct compression as per the formula shown in Table 1**.** The drug, polymers, and gums were mixed for 5 min in mortar with pestle according to geometric spatulation method, except magnesium stearate which was added at last and mixed before passing the mixture through sieve no: 60. Finally the mixture was compressed using 8.5 mm concave shaped punches in Elit Jemkay Engineers tablet punching machine to get biconvex

tablets of 255-325 mg weight[16,17]. The resulting matrix tablets were subjected to various evaluation parameters.

Table 1: Formulations of matrix tablets of Erythromycin stearate using different polymer combinations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	Target
Erythromycin Stearate	150	150	150	150	150	150	150	150	500
HPMC K 15 M	20	20	20	20	20	30	20	20	60
Chitosan	20	-	55	-	47	35	55	30	95
Xanthan Gum	20	-	-	55	-	-	-	-	-
Sodium Alginate	-	-	-	-	8	-	-	-	-
Hydroxy ethyl cellulose	10	10	10	10	10	-	10	10	30
Micro crystalline cellulose	85	85	30	30	30	50	70	30	90
Talc	9	9	9	9	9	9	9	9	15
Magnesium stearate	6	6	6	6	6	6	6	6	10
Total	**325**	**285**	**280**	**280**	**280**	**280**	**300**	**255**	**800**

Target Formulation = Marketed formulation, Total weight of the tablets is different because of density of the polymer (chitosan) and F 8 is my optimized formulation which contain less polymers with less binder.

Evaluation:

The following post compression parameters[18] are carried out on each batches of Controlled release tablets.

Appearance:

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture etc.

Weight variation:

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight. The tablet weight for extended release tablet is 350.00 mg and the maximum percent difference allowed is 7.5% i.e. ± 26.25 mg, for immediate release tablet, tablet weight is 140.00 mg and the maximum percent difference allowed is 7.5% i.e. ± 10.50 mg & for bilayer tablet, tablet weight is 490.00 mg and the maximum percent difference allowed is 5% i.e. ± 24.25 mg.

Thickness:

Tablet was selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within a ± 0.5% variation of standard value.

Friability Test:

Friability of the Immediate Release Tablets & Bilayer Tablets was determined using Friability Tester made by Electro lab. Friability for the IR tablets was determined for 100 revolutions while

friability for the bilayer tablets was determined for both 100 revolutions & 200 revolutions. Friability of the tablets should be less then 1%.

Hardness:

Tablet was selected at random from individual formulations and hardness was measured using Scheluniger hardness tester.

Dissolution Test:

The tablets were evaluated for *in vitro* drug release was carried out by using USP dissolution apparatus.

Dissolution test apparatus: USP type I (Electrolab TDT-08L)

Speed: 50 rpm

Stirrer: Basket type

Volume of medium: 900 ml

Volume withdrawn: 5 ml

Medium used: 0.1N HCl for first 2 hr, phosphate buffer pH 6.8 till 24 hr

Temperature: 37 ± 0.50 C

Analysis Of Release Mechanism

The *in vitro* dissolution data mentioned in Table No.6 was fitted to zero order, first order, Higuchi release model and Korsemeyer Peppas model to analyze the mechanism of drug release from the matrix tablets(Table 2).

Table 2: Equations used to compare dissolution profiles.

Method	Parameter/equation
Zero order	% dissolution =kt
First order	% dissolution =100(1- e^{-kt})
Higuchi	%dissolution= $kt^{0.5}$
Korsemeyer-Peppas model	Mt/Mt^{n}

[a] m_α is the initial drug amount (100%, when represented as percentage);
m_t the amount of drug remaining at a specific time (calculated as percentage of m_α);
k the rate constant; t is the time

RESULTS AND DISCUSSION

Table 3 gives information about Evaluation of pre-compression parameters of Erythromycin stearate bland.

The compatibility study was also carried out using the FT-IR. The FT-IR graphs of drug alone and also of both drugs and polymer were taken. There were not any extra peaks found in all cases so finally it was concluded that the excipients were compatible with drugs (Figure 1-5).

Table 3: Angle of repose, loose bulk density, Tapped bulk density and Carr's compressibility index

Batch	Angle of	Bulk	Tapped	Carr's	Hausner's
F1	$35^0$07'	0.4098	0.4889	16.17	1.19
F2	$32^0$31'	0.3873	0.4541	14.71	1.17
F3	$31^0$47'	0.4279	0.5065	15.51	1.18
F4	$30^0$25'	0.4211	0.5071	16.95	1.20
F5	$31^0$13'	0.4148	0.4880	15.0	1.17
F6	$20^0$79'	0.4035	0.4720	14.51	1.16
F7	$29^0$30'	0.4141	0.4641	10.77	1.12
F8	$30^0$15'	0.3869	0.4476	13.56	1.15
Target	$29^0$15'	0.4047	0.4782	14.79	1.16

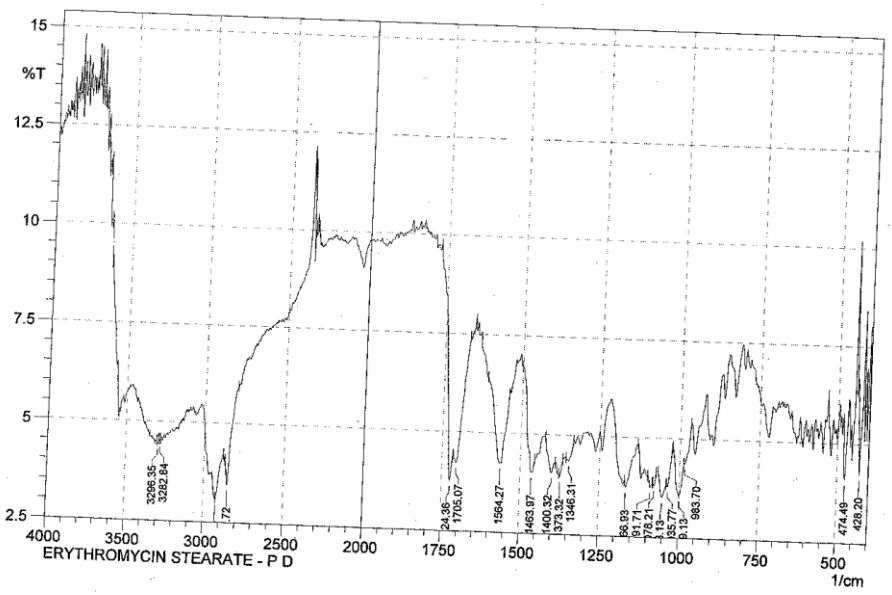

Figure 1: FTIR Spectrum of Erythromycin stearate

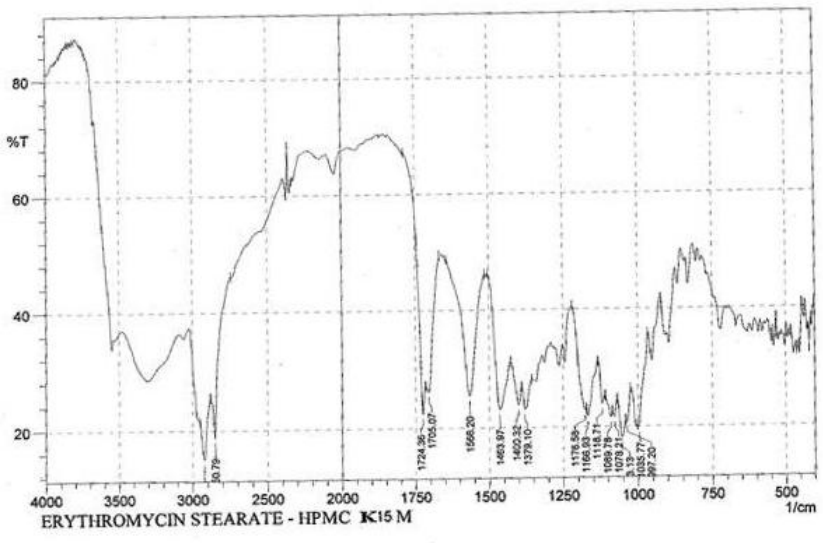

Figure 2: FTIR Srectrum of Erythromycin stearate with HPMC K 15M

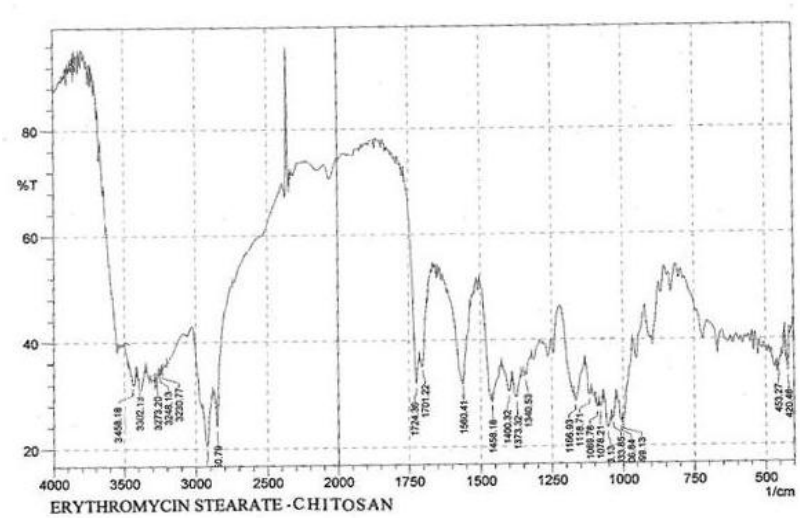

Figure 3: FTIR Srectrum of Erythromycin stearate with Chitosan

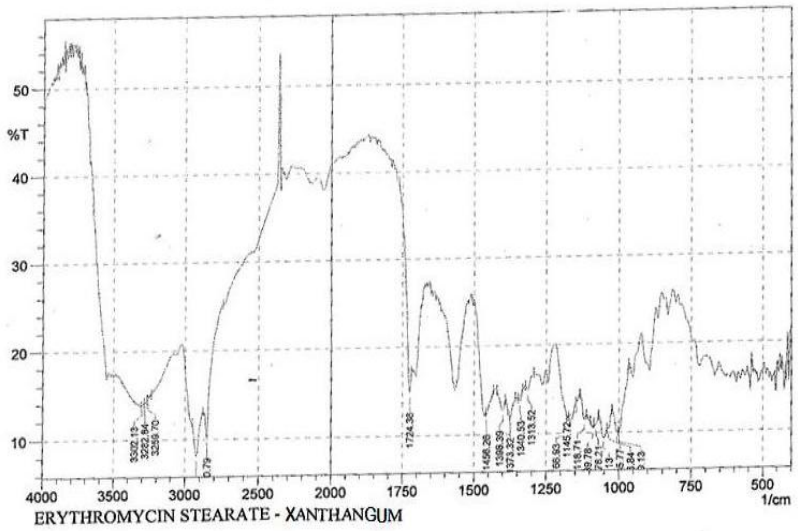

Figure 4: FTIR Srectrum of Erythromycin stearate with Xanthan gum

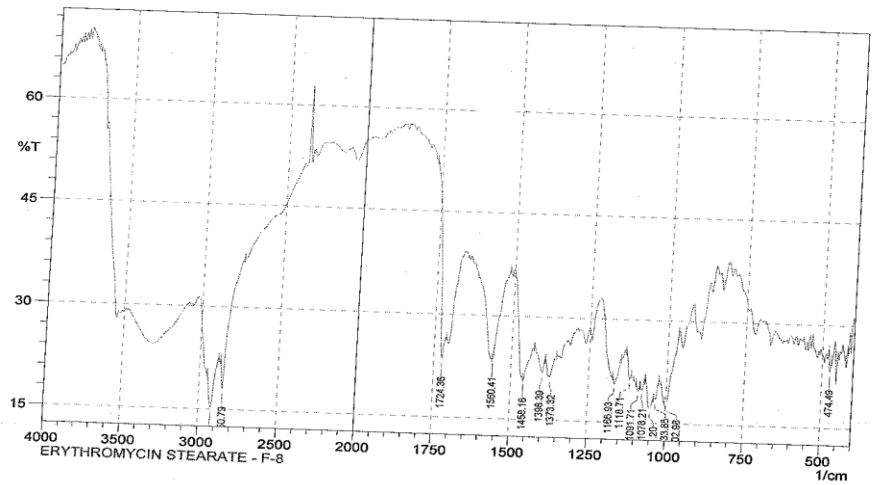

Figure 5: FTIR Srectrum of Optimised formulation (F8)

The Hardness of the tablets ranged between 4.0 Kg/Cm^2 to 6.5 Kg/Cm^2, the Thickness of the tablets ranged between 5.30mm to 5.50mm. The percent friability of the prepared tablets was well within acceptable limit. There was no significant weight variation observed between average weight and individual weight. The results showed in Table 4 indicated that the tablets possessed enough mechanical strength to maintain their integrity.

Table 4: Evaluation parameters of prepared Erythromycin stearate matrix tablets

Formulation	Evaluation Parameters					
	Thickness±SD (mm) (n=10)	**Diameter± SD (mm) (n-10)**	**Hardness±SD (kg/cm2) (n=5)**	**Friability %**	**Average weight variation (n=20) mg**	**Drug content %**
F 1	5.44±0.030	9.45±0.007	6.5±0.625	0.51	327±8.06	70.17
F 2	5.45±0.023	9.44±0.013	6.2±0.344	0.30	276±10.1	104.44
F 3	5.43±0.027	9.46±0.023	4.7±0.225	0.15	281±7.34	93.33
F 4	5.45±0.019	9.45±0.021	4.5±0.359	0.20	279±8.12	95.55
F 5	5.44±0.030	9.43±0.009	4.7±0.334	0.17	281±7.98	102.22
F 6	5.46±0.025	9.45±0.014	4.1±0.467	0.24	280±9.15	88.88
F 7	5.44±0.030	9.46±0.019	5.5±0.245	0.21	299±5.67	86.66
F 8	5.43±0.024	9.44±0.017	4.2±0.178	0.24	254±7.87	97.77
Target Formulation	5.30±0.026	14.24±0.013	5.8±0.876	0.18	801±8.12	96.22

The *in vitro* dissolution data showed in Table 5 and Figure 6 for Erythromycin stearate matrix tablets and comparison of Optimized formulation and Target release data showed in Figure 7. Various kinetic models were plotted as shown in the Figure 8-11. In Zero order r^2 value was 0.9625 and in first order r^2 value was 0.918 describing the drug release rate is independent of concentration of drug. The best linearity was found in Zero order (Figure 8, r^2 =0.9625) indicating the release of drug from matrix tablet based on super case II transport.

Table 5: *In vitro* dissolution profile

Time in Hour	Formulation code								
	F 1	**F 2**	**F 3**	**F 4**	**F 5**	**F 6**	**F 7**	**F 8**	**Target formulation**
1	15.0	3.7	3.6	2.1	2.8	6.3	4.2	2.5	2.0
2	17.5	7.3	6.4	5.6	4.7	6.7	5.2	4.1	2.5
3	16.6	8.9	7.1	7.0	5.2	8.2	6.6	4.5	5.1
4	18.9	21.0	8.1	10.6	7.0	8.6	7.3	7.1	7.4
5	19.6	32.8	15.4	12.4	12.0	9.2	12.4	10.8	10.1
6	20.7	53.7	17.9	14.1	13.8	16.3	15.2	14.1	18.9
12	21.2	97.3	47.5	53.6	43.2	57.9	49.4	42.0	48.6
18	31.4	-	82.0	82.4	91.5	82.2	81.2	91.7	88.2
24	38.9	-	87.5	93.2	97.9	85.8	85.4	97.2	95.0

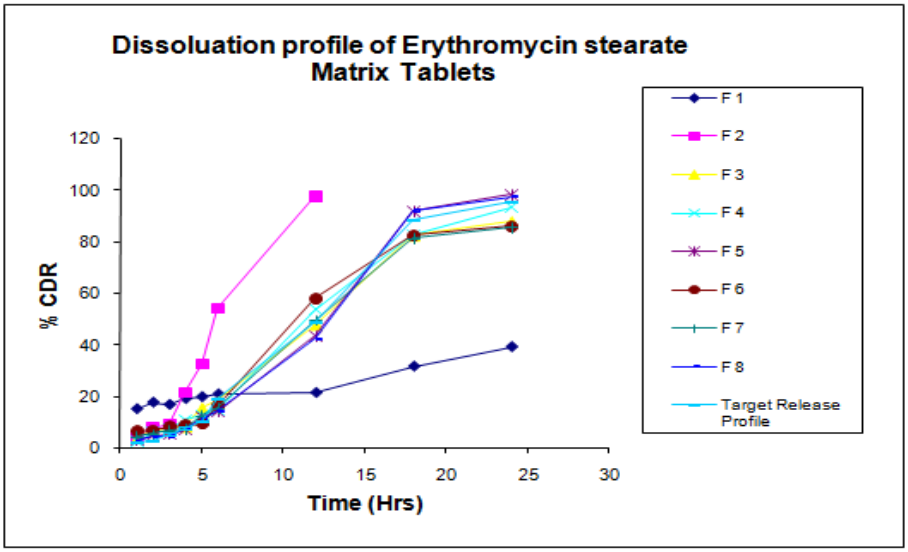

Figure 6: *In vitro* drug release profile of Erythromycin stearate matrix tablets

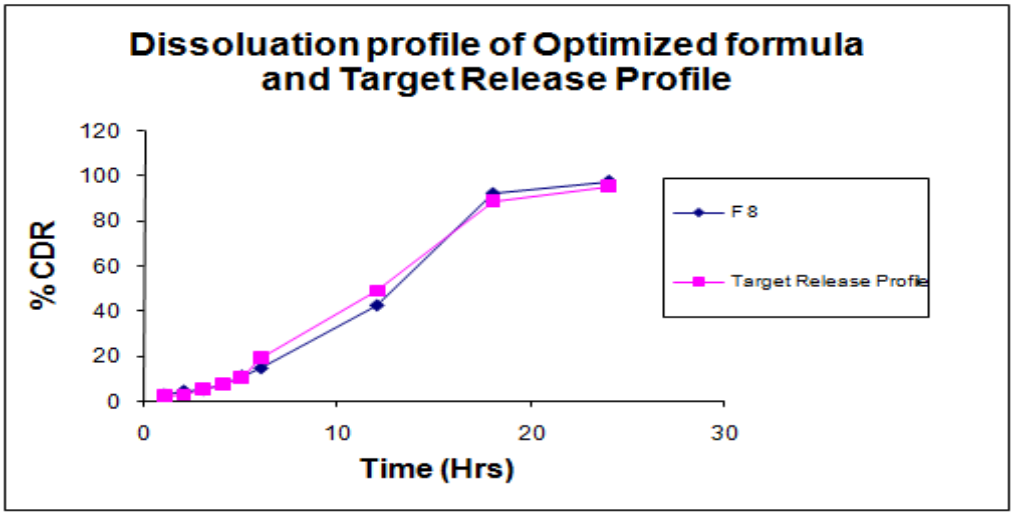

Figure 7: *In vitro* drug release profile of Optimized formula and Target release profile

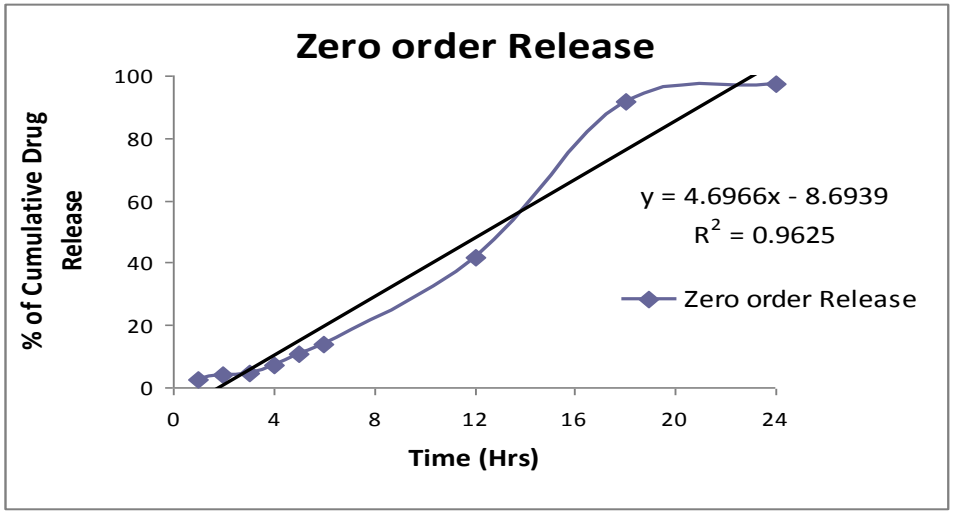

Figure 8: Zero order release model of Optimized formulation

Figure 9: First order release model of Optimized formulation

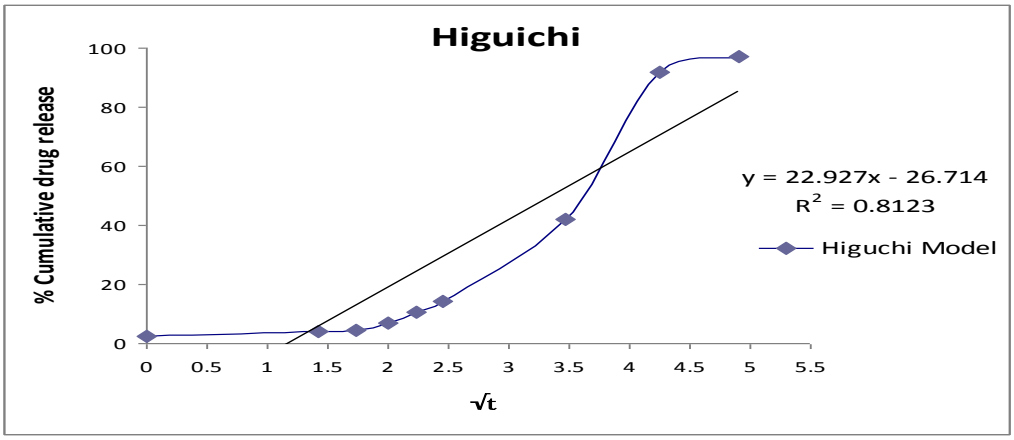

Figure 10: Higuchi release model of Optimized formulation

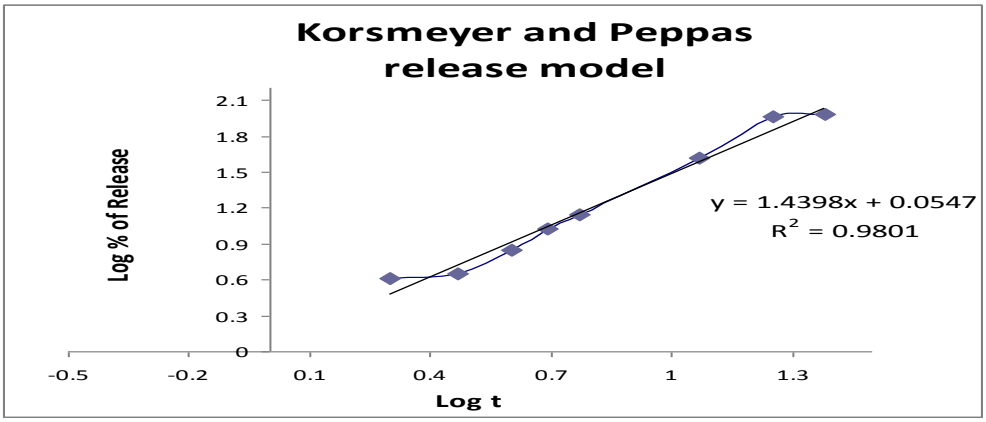

Figure 11: Korsmeyer and peppas release model of Optimized formulation

CONCLUSION

From the present experimental results it can be concluded that the formulation prepared in combination with HPMC K15M and Chitosan (F8) showed better similarity to the target formulation and has been optimized. The powder blend of the mixture of Erythromycin stearate, HPMC K15M, Chitosan, Xanthan gum and other excipients has a good flow property and

compressibility index. The overall drug release of the optimized formulation is more than that of the target release profile formulation but it has comparatively similar release pattern compared to target release profile formulation. The release of Erythromycin stearate from matrix tablet is in a controlled manner. Controlled drug release following Zero order release kinetics of Erythromycin stearate matrix tablets prepared from the polymers HPMC K15M, Chitosan and Xanthan gum can be successfully employed as a once daily oral controlled drug delivery dosage form.

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